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A New Paradigm for Type 2 Diabetes Mellitus

Could It Be a Disease of the Foregut?

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Summary Background Data

We previously reported, in a study of 608 patients, that the gastric bypass operation (GB) controls type 2 diabetes mellitus in the morbidly obese patient more effectively than any medical therapy. Further, we showed for the first time that it was possible to reduce the mortality from diabetes; GB reduced the chance of dying from 4.5% per year to 1% per year. This control of diabetes has been ascribed to the weight loss induced by the operation. These studies, in weight-stable women, were designed to determine whether weight loss was really the important factor.

Methods

Fasting plasma insulin, fasting plasma glucose, minimal model-derived insulin sensitivity and leptin levels were measured in carefully matched cohorts: six women who had undergone GB and had been stable at their lowered weight 24 to 30 months after surgery *versus* a control group of six women who did not undergo surgery and were similarly weight-stable. The two groups were matched in age, percentage of fat, body mass index, waist circumference, and aerobic capacity.

Results

Even though the two groups of patients were closely matched in weight, age, percentage of fat, and even aerobic capacity, and with both groups maintaining stable weights, the surgical group demonstrated significantly lower levels of serum leptin, fasting plasma insulin, and fasting plasma glucose compared to the control group. Similarly, minimal model-derived insulin sensitivity was significantly higher in the surgical group. Finally, self-reported food intake was significantly lower in the surgical group.

Conclusions

Weight loss is not the reason why GB controls diabetes mellitus. Instead, bypassing the foregut and reducing food intake produce the profound long-term alterations in glucose metabolism and insulin action. These findings suggest that our current paradigms of type 2 diabetes mellitus deserve review. The critical lesion may lie in abnormal signals from the gut.

Surgery has become the therapy of choice for morbid obesity, the most severe form of obesity, a disease in which patients usually exceed their ideal weight by at least 100 lbs. The usual approaches to weight loss—diets, medications, behavioral modification, and exercise—only rarely achieve significant long-term weight loss in these cases. In contrast, the gastric bypass operation (GB), probably the most commonly performed bariatric procedure, produces an average weight loss of 100 lbs that is maintained for as long as 14 years (Table 1).[1]

Weight control, however, is not usually the primary goal of bariatric surgery. Most commonly, patients are referred for control of the comorbidities of their massive obesity: diabetes, cardiopulmonary failure, hypertension, arthritis of weight-bearing joints, infertility, endocrine disorders, and an inability to carry out the tasks of daily living, such as personal hygiene. The approach is effective, with relief of

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Table 1. WEIGHT LOSS IN 608 MORBIDLY OBESE PATIENTS AFTER THE GASTRIC BYPASS OVER 14 YEARS WITH 97% FOLLOW-UP

	Mean Weights (lb) (range)	% Excess Weight Loss (range)	Body Mass Index
Before surgery	304.4 (198–615)	0.0	49.7 (33.9–101.6)
1 year	192.2 (104–466)	68.9 (10.3–124)	31.5 (19.1–69.3)
5 years	205.4 (107–512)	57.7 (−14.6–115.9)	33.7 (19.6–7.16)
10 years	206.2 (130–388)	54.7 (−0.9–103.1)	34.7 (22.5–64.7)
14 years	204.7 (158–270)	49.2 (7.2–80.9)	34.9 (25.9–54.6)

cardiopulmonary failure in almost all and hypertension in two thirds, improvement in mobility in the great majority, and return to gainful employment for many.

The most intriguing effect of GB, however, is the rapid and dramatic control of type 2 diabetes mellitus. We documented this remarkable effect in three separate studies.

In our 14-year follow-up study of the Roux-en-Y gastric bypass with a 97% follow-up, 121 of 146 (82.9%) diabetic morbidly obese patients and 150 of 152 (99%) morbidly obese patients with impaired glucose tolerance reverted to and maintained normal levels of plasma glucose, plasma insulin, and glycosylated hemoglobin.[1]

We also compared the effect of GB on two matched groups of morbidly obese patients with "occult" diabetes, defined as no previous history or diagnosis of diabetes, a fasting plasma glucose level greater than 140 mg/dL, and a plasma glucose level greater than 200 mg/dL 2 hours after a meal. Of the 61 patients, 50 underwent GB; the other 11 did not undergo surgery either because of personal reasons or their insurance companies' failure to approve the procedure. The two groups were comparable in age, weight, and fasting plasma glucose levels. After a follow-up of 8 years in the nonoperated group and 10.2 years in those who underwent GB, 6 of 11 (55%) of the control group developed type 2 diabetes compared to 0 of 50 of those who had the operation ($p < 0.0001$).[2]

Finally, we reviewed the outcomes of 232 morbidly obese patients with type 2 diabetes mellitus who were referred to East Carolina University between March 5, 1979, and January 1, 1994. Of these, 154 had the Roux-en-Y GB and 78 did not undergo surgery because of personal preference or their insurance companies' refusal to pay for the procedure. Patients who were refused on the basis of risk or intercurrent disease were excluded from the study. The surgical and the nonoperative (control) groups were comparable in terms of age, weight, body mass index, sex, and percentage with hypertension. The percentage of control subjects being treated with oral hypoglycemics or insulin increased from 56.4% at initial contact to 87.5% at last contact ($p < 0.0003$), whereas the percentage of surgical patients requiring medical management fell from 31.8% preoperatively to 8.6% at last contact ($p < 0.0001$). Further, the mortality rate was 28% in the control group *versus* 9% in the surgical group, including perioperative deaths. For every year of follow-up, the chance of dying was 4.5% for patients in the control group *versus* 1.0% for those in the surgical group.[3] The comparison provided the first demonstration in the literature that GB not only reversed the diabetes in most patients but also decreased mortality from the disease. In fact, to our knowledge, it is the first demonstration that any therapy could reduce the mortality from type 2 diabetes mellitus.

Weight loss—reduction of the fat mass induced by GB—has been generally accepted as the best explanation for the control and, indeed, the reversal of the diabetes mellitus. Our observations, however, demonstrate that the improvement in glucose and insulin levels occurs quickly, within days after GB, long before there is significant weight loss. Accordingly, the present studies, in two cohorts of weight-stable women, were designed to assess the role of weight loss in the return to euglycemia.

METHODS

Subjects

Fasting plasma glucose, fasting plasma insulin, leptin, and glycosylated hemoglobin levels, as well as minimal model-derived insulin sensitivity and aerobic capacity, were measured in two carefully matched weight-stable cohorts: the surgical group, six women who had undergone GB and had been stable at their lowered weight 24 to 30 months after surgery, and the control group, six women who did not undergo surgery and were similarly stable at the same weight as the GB patients.

All patients were weight-stable (±2 kg) for a minimum of 6 months, as documented in medical records, before testing. In addition, all women were nonsmokers, were free from known cardiovascular disease, orthopedic problems, and diabetes, and were not taking any medications that would interfere with carbohydrate metabolism. The two groups were matched (surgical *vs.* control) in age (40.4 ± 1.4 *vs.* 41.2 ± 1.1 years), percentage of fat (40.7 ± 1.6 *vs.* 40.2 ± 2.4), body mass index (39.6 ± 2.8 *vs.* 43.7 ± 4.6), waist circumference (122.3 ± 5.4 *vs.* 114.7 ± 4.5 cm), and aerobic capacity (VO_2max: 20.5 ± 1.5 *vs.* 20.1 ± 1.2 mL/kg/min). Descriptive characteristics are presented in Table 2.

The experimental procedures were approved by the Institutional Review Board for human research before initiating data collection.

Table 2. DESCRIPTIVE CHARACTERISTICS OF GASTRIC BYPASS AND CONTROL (CON) PATIENTS BEFORE THE STUDY

Variable	GB		CON
	Pre-Op	Post-Op	
Age		40.7 ± 1.6	40.2 ± 2.4
Mass (kg)	152.1 ± 8.8	107.7 ± 7.2*	98.2 ± 2.8
Fat mass (kg)	78.8 ± 7.9	45.5 ± 4.7*	41.9 ± 3.5
FFM (kg)	73.1 ± 1.6	62.4 ± 3.0*	56.3 ± 1.5§
% Fat	51.1 ± 4.4	40.7 ± 1.6*	40.2 ± 2.4
BMI ($kg \cdot m^{-2}$)	56.2 ± 4.4	39.6 ± 2.8*	43.7 ± 4.6
Waist (cm)	143.6 ± 6.5	122.3 ± 5.4*	114.7 ± 4.5
Aerobic Capacity(VO_2max)†		20.5 ± 1.5	20.1 ± 1.2

N = 6 in each group. Gastric bypass (GB) patients were studied 24 to 30 months after surgery. Preoperative data for the GB patients were obtained from patients' records. All patients were weight stable (±2 kg) for at least 6 months before participation in this investigation.
*$p < 0.05$ *vs* Pre-Op.
§$p < 0.05$ *vs* GB.
† Aerobic capacity (VO_2max) was measured in $mL \cdot kg^{-1} \cdot min^{-1}$.

Intervention

The GB procedure (Fig. 1) was performed in an identical manner on each of the operated subjects. The abdomen was entered through a midline incision. After an exploration demonstrated no contraindications to proceeding with the operation, the stomach was partitioned with two superimposed transverse staple lines, placed with a TA-90 stapling device, to produce a 20- to 30-mL proximal pouch. (We currently use three superimposed staple lines, as recommended by Sugerman [personal communication], because the additional application has decreased our staple line breakdown rate from 16% to 2%.) The jejunum was divided about 40 cm beyond the ligament of Treitz with a stapling device (GIA) and both ends were oversewn with a 3-0 braided absorbable suture (Vycril). The distal loop of jejunum was brought up through the mesocolon and the lesser sac for an 8- to 10-mm gastrojejunostomy with a double-layered, continuous anastomosis sewn with a 3-0 monofilament polypropylene suture (Prolene). The 60-cm loop Roux-en-Y was completed with a stapled jejunojejunostomy carried out with the GIA and TA-55 stapling devices. All staple lines were oversewn with the 3-0 absorbable braided suture to prevent anastomotic hemorrhage.

Intravenous Glucose Tolerance Test

A modified intravenous glucose tolerance test was performed after an overnight fast as previously described.[4] All such tests were administered at 7 a.m. Blood samples were analyzed spectrophotometrically for glucose (Sigma 16-UV, St. Louis, MO) and by microparticle enzyme immunoassay for insulin (IMx, Abbott Laboratories, Abbott Park, IL). Insulin sensitivity, glucose effectiveness, and first-phase insulin secretion were calculated using the MINMOD program of Bergman et al.[5]

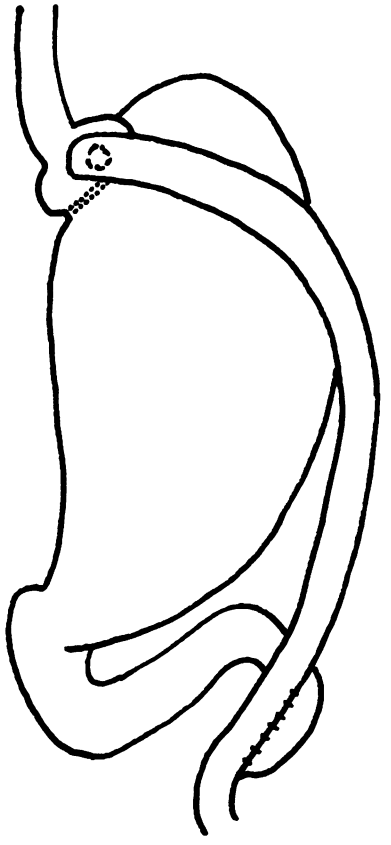

Figure 1. The normal stomach *versus* the GB procedure. GB alters the functions of the foregut significantly by limiting the amount of food, slowing its passage, and excluding the flow of nutrients from a major component of the gastrointestinal tract. These changes are produced with the creation of a gastric pouch of 20 to 30 mL, an 8- to 10-mm gastrojejunostomy, and a bypass of the antrum, duodenum, and proximal jejunum with a 60-cm Roux-en-Y loop.

Anthropometric Tests

Body density was determined by hydrostatic weighing after expiration to residual volume, as determined by oxygen dilution.[6] The percentage of body fat and fat-free mass were calculated from body density using the Siri equation.[7] Body mass was recorded to the nearest 0.1 kg and height to the nearest 0.1 cm. Body mass index was calculated as mass/height^2 (kg/m^2). Umbilicus, minimal waist, and maximal hip girths were obtained in duplicate as described by Lohman et al.[8] All circumferences were obtained with a spring-tension, stretchless Gulick tape (Lafayette Instruments, Lafayette, IN) to the nearest 1 mm. All measurements were obtained before and after exercise training.

Cardiorespiratory Fitness

VO_2max and time to exhaustion were determined during a physician-supervised incremental treadmill test before and after exercise training. Expired gases were monitored continuously (Sensormedics 2900, Anaheim, CA) to determine oxygen consumption. Exercise intensity was monitored periodically during training via the collection and analysis of expired gases.

Leptin Assay

Fasting serum leptin levels were determined using a commercially available radioimmunoassay kit (Linco Research, St. Charles, MO). Serum was not available for measurement of preoperative leptin levels.

Food Intake

Three-day (2 weekdays, 1 weekend day) food records were obtained from all patients. Patients were given detailed instructions regarding the use of the food records. Data were analyzed using Nutracalc Version 1.1.

Statistical Analysis

Data were analyzed using repeated measures analysis of variance. When significant interactions were obtained, the Scheffe procedure was used. Statistical significance was accepted as $p < 0.05$. All data are reported as mean ± standard error.

RESULTS

Results are summarized in Table 3

Table 3. RESULTS: COMPARISON OF METABOLIC INDICES IN GASTRIC BYPASS (GB) AND CONTROL (CON) PATIENTS

Variable	Control Subjects	After Gastric Bypass
Fasting glucose (mM)	5.70 ± 0.30	4.82 ± 0.14*
Fasting insulin (pM)	95.3 ± 9.7	23.0 ± 2.0*
Serum leptin (ng/ml^{-1})	35.8 ± 1.9	22.3 ± 2.3*
Leptin/unit fat mass**	0.96 ± 0.03	0.50 ± 0.03*
Minimal model derived		
Insuln sensitivity	1.75 ±0.45	3.90 ± 0.74*
Food Intake (Kcal/day^{-1})	2252 ±227*	1156 ± 146

* All values were significant at the $p < 0.05$ levels. Food intake was self-reported from the food records kept for 3 days.

Leptin

Serum leptin levels were significantly lower in the surgical *versus* the control group, both in absolute terms (22.3 ± 2.3 *vs.* 35.8 ± 1.9 ng/mL) and per unit fat mass (0.50 ± 0.03 *vs.* 0.96 ± 0.03 ng/mL/kg). In other words, leptin levels were approximately 40% lower in the surgical than in the control group ($p < 0.05$).

Insulin, Glucose, and Insulin Sensitivity

Levels of fasting plasma insulin (23 ± 2 *vs.* 95.3 ± 9.7 pM; $p < 0.05$) and fasting plasma glucose (4.82 ± 0.14 *vs.* 5.70 ± 0.30 mM; $p < 0.05$) were significantly lower in the surgical than in the control group. Minimal model-derived insulin sensitivity was significantly higher in the surgical than in the control group (3.90 ± 0.74 *vs.* 1.75 ± 0.45; $p < 0.05$). Glucose effectiveness and first-phase insulin secretion did not differ between the groups.

Diet Analysis

Self-reported food intake from 3-day diet records suggested that caloric intake was significantly less in the surgical than in the control group (1156 ± 146 *vs.* 2252 ± 227 Kcal/day; $p < 0.05$). No differences in macronutrient intake were observed (approximately 50% carbohydrate, 33% fat, 17% protein in each group).

Thus, stable weight loss subsequent to GB is associated with a reduction in the serum leptin level both in absolute terms and relative to fat mass. In addition, GB results in significant improvements in fasting insulin and glucose levels and whole body insulin sensitivity, despite the fact that the GB patients remain frankly obese.

DISCUSSION

Weight loss has generally been cited as the reason why GB provides such excellent and durable control of type 2 diabetes mellitus. We have doubted that explanation for two reasons. First, the return to euglycemia and normal insulin levels occurs within days after surgery (Figs. 2 and 3), long before there is any significant weight loss. Second, many of

Patient LT: Fasting Blood Glucose Levels and Insulin Requirements Before and After Gastric Bypass

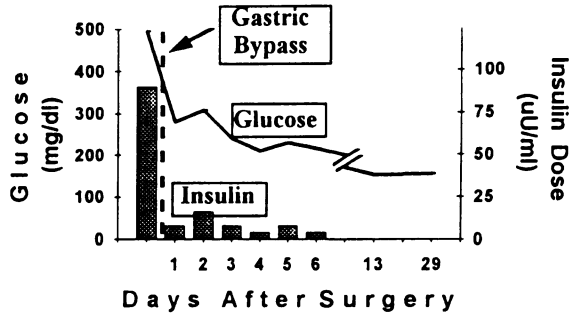

Figure 2. The response of a typical patient's glucose levels and insulin requirements, based on a sliding scale, after surgery shows that glucose insulin levels dropped to normal within days after GB.

our patients are still obese after the operation (a 400-lb woman may lose 150 lbs with a successful procedure, but at 250 lbs she is still obese), but their diabetes is controlled. If weight loss is not the reason for the control of the diabetes, two other explanations deserve consideration: decreased food intake and the exclusion of the antrum, duodenum, and proximal jejunum, parts of the foregut with dynamic endocrine activity.

The aim of this study, therefore, was to exclude weight loss as a variable. The two groups of women were of similar weight and had maintained that weight for at least 6 months. But even at the same weight, with identical fat mass and still obese, the women who had undergone GB had a return of plasma insulin, glucose, and even leptin to normal levels. Weight loss—that is, reduction in fat mass—is therefore not the cause for the correction.

The conclusion that weight loss *per se* is not the critical factor fits well with two observations of bariatric surgeons and dietitians: first, correction of abnormal diabetic indices occurs within days after surgery, before there is any significant reduction in fat mass, and second, a 5% weight loss, induced by a dietary program, is often enough to produce marked reductions in plasma glucose and insulin resistance, even though the patient is still obese. In our study, for example, GB returned insulin, glucose, and leptin levels back to normal even though the patients still had body mass indices of 39.6 ± 2.8, obese by any definition.

That conclusion leaves us with the remaining two variables as the explanation for the restoration of euglycemia and normal levels of insulin after GB: decreased food intake and the exclusion of the foregut—actually, two interdependent factors within the gut.

Accordingly, if decreased food intake and exclusion of the antrum, duodenum, and proximal jejunum control type 2 diabetes, it seems reasonable to conclude that the food and gut combination also plays a role in the genesis of the disease. Accordingly, it is our hypothesis that the continued overstimulation of the gut by food in vulnerable persons leads to overactive neuroendocrine signals to the islets. The beta cells respond with hyperinsulinemia, which in turn causes insulin resistance and interference with the insulin-dependent metabolic activities of the cells. With that view, insulin resistance may well be a protective phenomenon of the cells, and the lowered insulin output of the advanced diabetic becomes the result of exhaustion of the beta cells from the excessive stimulation. The hypothesis is also strongly supported by the following four observations.

First, most type 2 diabetics are obese or were obese at the onset of their disease. Second, patients with insulinomas, tumors that produce excessive amounts of insulin, are insulin-resistant. Third, a comparison of GB *versus* the vertical banded gastroplasty by Kellum and colleagues[9] showed that the latter patients had lesser reductions in hyperglycemia and hyperinsulinemia than the GB patients. They also noted that cholecystokinin, serotonin, and vasoactive intestinal polypeptide responses to meals were not altered by either operation. However, the 3-hour integrated enteroglucagon response to glucose increased markedly in GB patients, a response not seen in the gastroplasty patients. Finally, a sham operation in one of our patients, followed by the same stringent postoperative diet used in GB patients, produced a similar fall in plasma glucose and insulin as in the GB patients. (This patient had a massive meal the night of surgery, leaving him with a full stomach at the time of exploration. We did not perform GB because we thought that stapling could be compromised. Instead we closed and, after he recovered, asked him to cooperate with us by adhering to the same postoperative diet that we used for the GB patients. He did so for several weeks, and during this period he had the same improvement in plasma glucose and insulin levels as the patients who had the bariatric procedure.)

The suggestion that the gut plays an important role in glucose metabolism and insulin action is not new. In fact, it has long been known that oral glucose induces a greater insulin response than intravenous glucose, a difference attributed to the secretion of certain gut hormones called

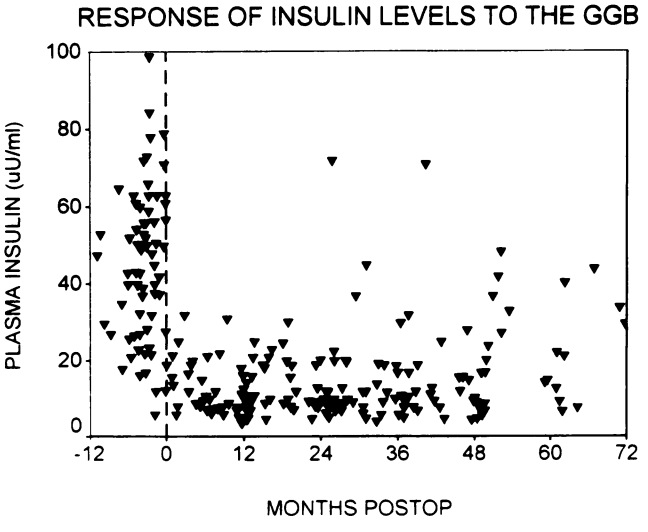

Figure 3. Insulin levels in a series of patients after GB. The hyperinsulinemia, a reflection of insulin resistance, disappears rapidly after GB.

incretins.[10–13] The most prominent incretins include glucagon, glucagon-like peptide 1 (7 to 36) (GLP-1), and glucose-dependent insulinotropic polypeptide, or gastric inhibitory peptide (GIP). GLP-1 is the most potent insulinotropic hormone known. It inhibits glucagon secretion, lowers blood glucose, inhibits gastrointestinal secretion and motility, and mediates the "ileal brake" effect (*i.e.*, the inhibition of upper gastrointestinal functions elicited by the presence of unabsorbed nutrients in the ileum).[14] The differences and overlap between GIP and GLP-1 are still being explored. For example, GIP levels increased significantly in response to oral glucose, whereas plasma levels of GLP-1 were unaffected.[15] The GIP gene is greatly expressed in the duodenum, jejunum, and ileum, with a continuous decrease from upper to lower intestines; however, the expression of the proglucagon gene encoding GLP-1 had an opposite appearance, with the highest expression in the large bowel and ileum.[16] It is likely that there are other incretins still to be discovered.

A particularly intriguing series of studies of the effect of the intestine on glucose metabolism was reported by Rudnicki et al.[17] They compared glucose tolerance curves in two rat preparations with Roux-en-Y procedures in which one was left as a blind loop and the other connected the blind end to the biliary tract. The animals with the blind, unconnected loop had significantly lower responses to the oral glucose tolerance test, with markedly lower glucose and insulin levels. The authors speculated that the blind bypass led to a GIP deficiency because "it appears that both the absorption of nutrients and the presence of all components of gastrointestinal chyme is essential for its release."

Another unexplained finding in this study is the ability of the GB subjects to maintain their weight with an intake of 1156 ± 146 Kcal/day, while the control group required almost twice as much food (2252 Kcal/day) to maintain theirs.

The search for a better explanation for type 2 diabetes is important. The disease is the leading cause of blindness, renal failure, and amputations in the United States, as well as a major cause of heart disease and strokes. With the increasing prevalence of obesity in our nation, to the point where one out of three Americans is obese, the incidence of diabetes has exploded in a similar fashion. Based on the National Health Interview Survey, there were approximately 7.8 million diagnosed cases of diabetes in the United States in 1993. The rate for all ages of 3.1% in 1993 was more than three times the prevalence of 0.93 in 1958, a period of 35 years.[18] It is likely that an equal number of Americans have the disease but remain undiagnosed.

There are several limitations of our study. First, our study group was small. Second, none of the GB patients had diabetes before their surgery. However, morbidly obese patients are insulin-resistant, and type 2 diabetes represents a more extreme example of that same metabolic abnormality. Our next study will address these two concerns with a larger group of patients who were diabetic before their bariatric surgery. Third, recall of dietary intake has only limited reliability, even though we did our best to make these as accurate as possible. The next study should be done in a metabolic unit capable of rigorous dietary documentation.

It is also possible that the differences between the study groups are not due to the surgery itself but to the fact that the GB group included subjects who were previously more obese and the control group included subjects at the zenith of their obesity. The lean person who was previously obese could present with a syndrome that is different from that in the never-obese lean subject. The basis for this concept lies in longitudinal studies of the Pima Indians that showed that the better the insulin sensitivity, the higher the rate of weight gain,[19] and the lower the leptin levels, the higher the rate of weight gain.[20]

CONCLUSIONS

Weight loss—that is, reduction in fat mass—does not solely account for the antidiabetic effects of GB. The operation probably controls hyperglycemia and hyperinsulinemia by diminishing food intake and bypassing the foregut, with its rich endocrine response. If type 2 diabetes mellitus can be controlled by the reduction of intake and the exclusion of a portion of the foregut, it seem reasonable to conclude that the disease may also have its origins in the gut. Accordingly, we believe that a new hypothesis deserves consideration and testing: that type 2 diabetes mellitus is due to an overstimulation of the pancreas by excessive gut signals, and that insulin resistance is a protective defense of the cell. If this hypothesis is correct, studies of the neuroendocrine signaling mechanisms between the gut and the islets could offer a productive new approach to our understanding of diabetes.

Acknowledgments

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Discussion

DR. HARVEY J. SUGERMAN (Richmond, Virginia): President Wells, Secretary Copeland. This is another thought-provoking study from Drs. Pories, Caro, and their colleagues at East Carolina University, which suggests that the foregut may be the culprit in Type II diabetes. They noted a decreased fasting glucose, a markedly decreased fasting insulin and serum leptin levels as well as serum leptin per unit of fat mass with a significantly increased insulin sensitivity in age, weight, energy expenditure matched, weight-stable gastric-bypassed women compared to control women.

I believe that the major finding, actually, in this study is the decreased serum leptin level per unit of fat-free mass, as leptin is supposedly manufactured by fat cells, the adipocytes. It is unfortunate that blood was not available in the gastric-bypass patients prior to their surgery to determine their preoperative glucose, insulin, and leptin status.

In a study presented to this Association in 1989 from our unit by Dr. Kellam, we also noted a marked decrease in insulin secretion and glucose levels following gastric bypass, which were much greater in the gastric bypass patients as compared to vertical-banded gastroplasty patients. However, some of this improvement could have been secondary to a better weight loss in the gastric bypass group at the time of their study. Sirinek and his colleagues from San Antonio also noted a marked improvement in insulin and glucose levels shortly after gastric bypass and in association with decreased GIP levels.

Now although these data are interesting, it seems to be a leap of faith to presume that the cause of Type II diabetes is secondary to abnormal gut peptide secretion in genetically susceptible patients. While this hypothesis is certainly plausible, further studies will be required. None of the women in the current study had Type II diabetes. I presume that Dr. Pories and his colleagues are now conducting a prospective study comparing pre- and early as well as late postoperative glucose insulin and leptin levels in both diabetic and nondiabetic obese patients who are undergoing gastric bypass, as well as those at East Carolina who are now undergoing the gastric restrictive procedure, adjustable laparoscopic gastric banding.

With regard to the intriguing leptin data, this study suggests that leptin levels may not be controlled only by the number and size of adipocytes, but also by either serum insulin levels or caloric intake. Obviously, these two effects are not mutually exclusive.

Does the greater delivery of glucose to the distal small bowel lead to secretion of other gut factors in addition to entero- glucagon as noted in our study, leading to a decreased secretion of leptin, which then may provide us a tidy signal to the CNS? Or are these merely epiphenomena as in contrast to the OBOB mice, where leptin is related to obesity, leptin has never been shown to have a satiety effect in humans where serum leptin levels are directly proportional to weight and fat mass?

Could the improved insulin sensitivity be due to a decreased circulation free fatty acid levels after gastric bypass, given the similar weight and fat mass in the two groups of patients studied by Dr. Pories? Were there differences in fat distribution between these two groups, that is, visceral fat *versus* peripheral or subcutaneous fat?

The concept that increased food in the foregut leads to increased islet stimulation via increased incretin production which then in turn leads to diabetes and that insulin resistance is a protective mechanism continues to be an intriguing hypothesis. The current study does not answer the question.

In summary, I believe that it is an exciting hypothesis that mandates further study, and I look forward to future reports from Dr. Pories and his colleagues. Thank you. [Applause]

DR. HENRY L. LAWS, JR. (Birmingham, Alabama): Dr. Wells, Dr. Copeland, Colleagues. I wish to congratulate the presenters on this very interesting work. I think all surgeons who have done some bariatric surgery recognize the dramatic deep improvement in diabetics, whether the patients have undergone a gastric bypass or a gastroplasty.

It is interesting that about 55% of their patients were either overtly diabetic or had impaired glucose metabolism before surgery. In the first 100 patients that I treated, I did a glucose tolerance test on them, and 65% were diabetic, by the curve. Conversely, all were alleviated of any evidence of diabetes postoperatively, and we quit testing patients.

In this era of cost containment, should we still test all patients for diabetes before undergoing bariatric surgery?

As suggested by Dr. Sugerman, I think a valuable study would be to test patients who have undergone gastroplasty in some fashion with those who have undergone gastric bypass. Because in